REMARKS

Claims 1-22 are pending in the instant application. Claims 1-22 stand rejected under 35 U.S.C. § 103(a) as being obvious over Wu *et al.*, Receptor-Mediated Gene Delivery *in Vitro*, J. Bio. Chem. v. 266 no. 22:14338-14342 (1991) ("Wu *et al.*") in view of U.S. Patent Number 5,230,883 to Kornguth *et al.* ("Kornguth *et al.*"). Claims 1-4, 6-10, 12, 13, 16, and 22 stand rejected under statutory double patenting over Claims 1-8, 12, and 21-23 of copending application Ser. No. 08/321,552. Claims 5, 11, 14, 15, and 17-21 stand rejected under obviousness-type double patenting over Claims 9-11, 24-27, and 35-38 of copending application Ser. No. 08/321,552.

Statutory Double Patenting

Applicants intend on canceling claims 2-11 and 13-36, and on amending Claims 1 and 12 in copending application Ser. No. 08/321,552. A copy of the pending claims of Ser. No. 08/321,552, as amended, will be forwarded to the Examiner after such amendments have been made. Applicants believe the cancellations and amendments will render moot the Statutory Double Patenting rejection of the presently pending claims. It is believed at this time that the Examiner will be in receipt of the amendments to the claims in Ser. No. 08/321,552 prior to considering the present response. Accordingly, Applicants respectfully request the Examiner to withdraw the statutory double patenting rejection of Claims 1-4, 6-10, 12, 13, 16, and 22.

Obviousness-Type Double Patenting

Applicants have canceled claims 2-11 and 13-36, and have amended Claims 1 and 12 in copending application Ser. No. 08/321,552. A copy of the pending claims of Ser. No. 08/321,552, as amended, will be forwarded to the Examiner after such amendments have been made. Applicants believe the cancellations and amendments will render moot the Statutory Double Patenting rejection of the presently pending claims. It is believed at this time that the Examiner will be in receipt of the amendments to the claims in Ser. No. 08/321,552 prior to considering the present response. Accordingly, Applicants respectfully request the Examiner to withdraw the obviousness-type double patenting rejection of Claims 5, 11, 14, 15, and 17-21.

Section 103 Rejections

The Examiner has rejected Claims 1-22 under 35 U.S.C. § 103(a) as being obvious over Wu *et al.* in view of Kornguth *et al.* Applicants traverse the rejection on the ground that the Examiner has failed to establish a *prima facie* conclusion of obviousness because, at a minimum, the required motivation or suggestion to combine the cited references is lacking.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g.*, *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable

expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims.

The Federal Circuit has repeatedly warned that the requisite motivation to combine or modify references must come from the prior art, not the applicant's specification. *See, e.g., In re Dow Chem. Co.*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). The mere fact that references can be modified does not render the resultant modification obvious unless the prior art also provides the motivation to combine or modify the references to arrive at the claimed invention. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Claims 1-15

Claim 1 recites, *inter alia*, (a) a first polymeric molecule having a net positive or negative charge; (b) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule; (c) at least one cell targeting moiety attached to said second polymeric molecule; and (d) at least one physiological agent attached to said first or second polymeric molecule.

The Examiner argues that Wu *et al.* teach a delivery vehicle comprising a cell-targeting moiety (*i.e.*, asiooglucosomoid) attached to poly-L-lysine, which is complexed with DNA. The Examiner indicated that Kornguth *et al.* has been relied upon only for the teaching that a DTPA-(physiological agent) complex can be attached to a polycation (*i.e.*, poly-L-lysine). The Examiner concludes, therefore, that it would have been obvious to simply attach the DTPA-(physiological agent) complex of Kornguth *et al.* to the delivery vehicle of Wu *et al.* to arrive at the claimed invention. Applicants disagree. At a minimum, the

Examiner has failed to establish the necessary motivation, which must come from the prior art, for combining or modifying the references to arrive at the claimed invention.

Wu *et al.* teach a DNA delivery vehicle that utilizes a cell targeting moiety to deliver the DNA to a cell possessing receptor unique to the cell targeting moiety. More specifically, Wu *et al.* teach attaching an asialoglycoprotein (asialoorosomucoid) to a polycation (poly-L-lysine) to form a positively charged asialoorosomucoid-(poly-L-lysine) conjugate, and then complexing the conjugate with the negatively charged DNA to form a substantially charge neutral asialoorosomucoid-(poly-L-lysine)-DNA complex. Wu *et al.* teach that the asialoorosomucoid of the complex specifically targets its unique hepatocyte receptor, thereby delivering the DNA to a particular cell via the cell's uptake mechanism for that receptor/targeting moiety.

Kornguth *et al.*, in distinct contrast to Wu *et al.*, teach delivering a physiological agent based upon an electrostatic charge difference between a delivery vehicle and tumor tissue. More specifically, Kornguth *et al.* teach attaching a linking molecule (*i.e.*, DTPA) to a positively charged polycation (*i.e.*, poly-L-lysine) to form a positively charged DTPA-(poly-L-lysine) conjugate, and then binding a physiological agent (*i.e.*, Gd, Mn or radioisotopes) to the DTPA of the conjugate, which forms a high net positive charged (DTPA-physiological agent)-(poly-L-lysine) complex. Significantly, Kornguth *et al.* teach that the high net positive charge is required to target the tumor cells. *See, e.g.,* Kornguth *et al.* at 2:6-11; 2:62-65; and 3:40-43.

Wu *et al.* provide no motivation to add a physiological agent to their delivery vehicle; Wu *et al.* do not even mention physiological agents. Korgnuth *et al.*, alone or in combination

with Wu *et al.*, do not provide the required motivation to combine the teachings of the two references. Kornguth *et al.* teach delivery of physiological agents, not DNA as taught by Wu *et al.* Additionlly, the vehicles of Kornguth *et al.*, in distinct contrast to those of Wu *et al.*, rely entirely upon a high net positive charge of the vehicle to target tumor cells. *See, e.g.,* Kornguth *et al.* at 2:6-11; 2:62-65; and 3:40-43. Adding negatively charged DNA to the net positive complex of Kornguth *et al.* would significantly reduce or eliminate the targeting capability thereof. Thus, Kornguth *et al.* teach a delivery mechanism, (*i.e.*, high net positive charge) that is substantially different from and incompatible with the delivery mechanism of Wu *et al.* (*i.e.*, a substantially charge neutral vehicle with a cell receptor targeting moiety). Therefore, Kornguth *et al.*'s requirement of a high net positive charge would lead a skilled artisan away from combining the two references. A reference leading away from a combination cannot provide the required motivation to make the combination.

The Examiner argues that the motivation to modify or combine Wu *et al.* with Korgnuth *et al.* comes by virtue that Wu *et al.* and Korgnuth *et al.* both utilize a positively charged poly-L-lysine cation as part of the respective delivery vehicles, and therefore, it would have been obvious to modify Wu *et al.* by simply attaching the DTPA-(physiological agent) complex of Kornguth *et al.* to the poly-L-lysine of the substantially charge neutral delivery vehicle of Wu *et al.* to arrive at the claimed invention.

The Examiner urges that the targeting mechanism of Kornguth *et al.* is not relevant to the present analysis because Kornguth *et al.* is a secondary reference. This is legally incorrect. The mere fact that references can be modified does not render the resultant modification obvious unless the prior art also provides the motivation to combine or modify

the references to arrive at the claimed invention. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01. The Examiner must consider a reference in its entirety for what it teaches. *See, e.g., Baush & Lomb v.* Barnes-Hind/Hydrocurve, 230 USPQ 416, 419 (Fed. Cir. 1986). "'It is impermissible . . . to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.'" *Id.* (*quoting* In *re Wesslau*, 147 USPQ 391, 393 (C.C.P.A. 1965)). The Examiner has ignored that the targeting mechanism of Kornguth *et al.* is substantially different from and incompatible with the charge neutral vehicle as taught by Wu *et al.* A reference that teaches away from a combination cannot provide the required motivation to combine the references.

Additionally, the Examiner has impermissibly relied upon the present invention in drawing the conclusion that a skilled artisan would be motivated to combine the teachings of Wu *et al.* with those of Kornguth *et al.* The present invention is the only reference to teach the desirability of a targeting delivery vehicle having, *inter alia*, (a) a first polymeric molecule having a net positive or negative charge; (b) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule; (c) at least one cell targeting moiety attached to said second polymeric molecule; and (d) at least one physiological agent attached to said first or second polymeric molecule. Only the present invention teaches the claimed combination would even be possible. "To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own

reconstruction–an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aeorsonic Corp.*, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

For these reasons the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claim1. In particular one of skill in the art would simply not have been motivated to combine the cited references. Neither reference, alone or in combination, provides the necessary motivation to combine the references. The Examiner failed to consider the references as a whole and impermissibly picked and chose elements using the Applicants' invention as a template for its own reconstruction.

Claims 2-15 ultimately depend from and necessarily contain each and every limitation of Claim 1. Thus, the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claims 2-15.

Claims 16-22

Claim 16 recites a method for delivering a nucleic acid to a cell by, *inter alia*, contacting the cell with a nucleic acid delivery vehicle. The delivery vehicle recited in Claim 16, similar to the delivery vehicle of Claim 1, comprises, *inter alia*, (a) a nucleic acid; (b) at least one first polycationic molecule complexed with the nucleic acid; (c) at least one cell targeting moiety for a surface receptor attached to the first polycationic molecule; and (d) at least one contrast agent attached to the first or second polycationic molecule. Claim 17 recites a method for delivering physiological agents to a cell by, *inter alia*, contacting the cell with a delivery vehicle.

The delivery vehicle recited in Claim 17, similar to the delivery vehicle of Claim 1, comprises, *inter alia*, (a) a first polymeric molecule having a net positive or negative charge;

(b) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule; (c) at least one cell targeting moiety for a surface receptor on the cell attached to said second polymeric molecule; and (d) at least one physiological agent attached to said first or second polymeric molecule.

For reasons described above, the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claims 16 and 17. In particular one of skill in the art would simply not have been motivated to combine Wu *et al.* and Kornguth *et al.* in the manner urged by the Examiner. Neither reference, alone or in combination, provides the necessary motivation to combine the references. The Examiner failed to consider the references as a whole, and impermissibly picked and chose elements from the references using the Applicants' invention as a template for its own reconstruction.

Claims 18-21 ultimately depend from and necessarily contain each and every limitation of one or both Claim 16 or 17. Thus, the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claims 16-21.

Claim 22

The Examiner has rejected Claim 22 under 35 U.S.C. § 103(a) as being obvious over Wu *et al.* in view of Kornguth *et al.* Applicants traverse the rejection. The Examiner has failed to establish a *prima facie* conclusion of obviousness for the reasons described above, *i.e.*, the required motivation or suggestion to combine the cited references is lacking. Additionally, the Examiner has failed to establish a *prima facie* conclusion of obviousness on

the additional ground that the references, alone or in combination, do not teach each and every element of the claimed invention.

Claim 22 recites a delivery vehicle comprising, *inter alia*, (a) a first polymeric molecule having a net positive charge and having hydrophobic residues that facilitate cellular uptake of said delivery vehicle; (b) a second polymeric molecule having a net negative charge and complexed with said first polymeric molecule; and (c) at least one physiological agent attached to said first or second polymeric molecule.

A thorough discussion of Wu *et al.* and Kornguth *et al.* is provided above, and will not be repeated here for sake of brevity. In addition to the fact that the required motivation to combine Wu *et al.* and Kornguth *et al.* is lacking, neither of these references, alone or in combination, even mention using hydrophobic residues attached to a first polycationic molecule as recited in Claim 22.

Thus, the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claim 22, because (a) the cited references, alone or in combination, fail to provide the required motivation to combine the same, and (b) the cited references, alone or improperly combined, fail to teach or suggest each and every element of the claimed invention.

Conclusion

For the reasons given above, the Examiner has failed to establish a *prima facie* conclusion of obviousness against Claims 1-22. More specifically one of skill in the art would simply not have been motivated to combine the cited references. Neither reference, alone or in combination, provides the necessary motivation to combine the references. The

Examiner failed to consider the references as a whole and impermissibly picked and chose elements using the Applicants' invention as a template for its own reconstruction. Additionally with respect to Claim 22, neither reference, alone or in combination, teaches or suggests each and every element of the claim. Accordingly, Applicants respectfully request that the rejection of Claims 1-22 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the now pending claims are in condition for allowance. An early notification to that effect is respectfully requested. If a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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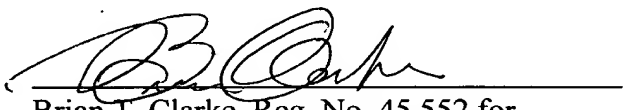

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Appendix A
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APPENDIX A:

1. A delivery vehicle comprising:

   a) a first polymeric molecule having a net positive or negative charge,

   b) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule, said second polymeric molecule having attached thereto at least one cell targeting moiety, and

   c) at least one physiological agent attached to said first or second polymeric molecule or to a third polymeric molecule, wherein said third polymeric molecule, if present, has a net charge opposite that of said first polymeric molecule and is complexed with said first polymeric molecule.

2. A delivery vehicle according to claim 1 wherein said first polymeric molecule comprises a nucleic acid.

3. A delivery vehicle according to claim 2 wherein said nucleic acid is DNA.

4. A delivery vehicle according to claim 3 wherein said DNA encodes a polypeptide.

5. A delivery vehicle according to claim 3 wherein said polypeptide is herpes thymidine kinase protein.

6. A delivery vehicle according to claim 2 wherein said second polymeric molecule comprises a polyamine.

7. A delivery vehicle according to claim 6 wherein said third polymeric molecule is present and comprises a polyamine.

8. A delivery vehicle according to claim 6 wherein said second polymeric molecule is selected from the group consisting of polylysine and spermidine.

9. A delivery vehicle according to claim 7 wherein said second polymeric molecule comprises polylysine or spermidine and said third polymeric molecule comprises polylysine or spermidine.

10. A delivery vehicle according to claim 1 wherein said physiological agent comprises a contrast agent.

11. A delivery vehicle according to claim 10 wherein said contrast agent comprises a paramagnetic ion complexed with a chelator.

12. A delivery vehicle according to claim 11 wherein said paramagnetic ion is gadolinium.

13. A delivery vehicle according to claim 12 wherein said chelator comprises diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclo-dodecane-N,N′,N′′,N′′′ tetracetic acid (DOTA).

14. A delivery vehicle according to claim 1 wherein said physiological agent is a therapeutic agent.

15. A delivery vehicle according to claim 14 wherein said therapeutic agent is a selected from the group consisting of phototherapeutic agents and anti-cancer agents.

16. A method of delivering a nucleic acid to a cell comprising:

(a) contacting said cell with a nucleic acid delivery vehicle comprising:

i) a nucleic acid,

ii) at least one first polycationic molecule complexed with said nucleic acid, said first polycationic molecule having attached thereto at least one cell targeting moiety for a surface receptor on said cell, and

iii) at least one contrast agent attached to said first polycationic molecule or to a second polycationic molecule, wherein said second polycationic molecule, if present, is complexed with said nucleic acid, and

(b) detecting the presence of said contrast agent in said cell as an indication of whether said nucleic acid has been delivered to said cell.

17. A method of delivering physiological agents to a cell comprising:

a) contacting said cell with a delivery vehicle comprising:

i) a first polymeric molecule having a net positive or negative charge,

ii) at least one second polymeric molecule having a net charge opposite that of said first polymeric molecule and complexed with said first polymeric molecule, said second polymeric molecule having attached thereto at least one cell targeting moiety for a surface receptor on said cell, and

iii) at least one physiological agent attached to said first or second polymeric molecule or to a third polymeric molecule, wherein said third polymeric molecule, if present, has a net charge opposite that of said first polymeric molecule and is complexed with said first polymeric molecule; and

b) detecting the presence of said physiological agent in said cell as an indication of whether said physiological agent has been delivered to said cell.

18. A method according to claim 17 wherein said physiological agent is a contrast agent.

19. A method according to claim 17 wherein said physiological agent is a therapeutic agent.

20. A method according to claim 17 wherein said delivery vehicles comprise at least one contrast agent and at least one therapeutic agent.

21. A method according to claim 18 or 20 wherein said detection is by magnetic resonance imaging (MRI).

22. A delivery vehicle comprising:

a) a first polymeric molecule having a net positive charge and having hydrophobic residues that facilitate cellular uptake of said delivery vehicle,

b) a second polymeric molecule having a net negative charge and complexed with said first polymeric molecule, and

c) at least one physiological agent attached to said first or second polymeric molecule.